



# PATENT SPECIFICATION

DRAWINGS ATTACHED

1110,360

Inventors: ROLAND-YVES MAUVERNAY and NORBERT BUSCH

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Int. Cl.:—C 07 d 99/02

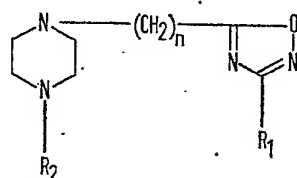
## COMPLETE SPECIFICATION

### Piperazine Derivatives and preparation thereof

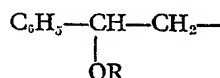
I, ROLAND-YVES MAUVERNAY, a French citizen of 63 Riom, France, do hereby declare the invention for which I pray that a patent may be granted to me, and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention is concerned with a novel class of piperazine derivatives and with a process for their preparation.

I have found that piperazine derivatives of the formula



in which  $R_1$  is a phenyl, 4-fluorophenyl, 3,4,5-trimethoxyphenyl, furyl, thienyl, 3-pyridyl or 4-pyridyl group;  $R_2$  is a phenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, a phenyl-alkoxyethyl group of the formula



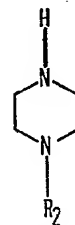
(in which R is an alkyl group containing 1 to 4 carbon atoms, particularly methyl, ethyl or isobutyl), or a benzyl group; and  $n$  is 1, 2 or 3, and their addition salts with physiologically acceptable acids, have valuable anti-inflammatory and analgesic properties.

According to the present invention, therefore, there are provided, as new compounds, piperazine derivatives of the above formula and their physiologically acceptable acid

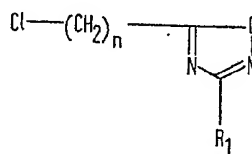
[Price 4s. 6d.]

addition salts. The present invention also comprises pharmaceutical compositions comprising one or more of the compounds according to the invention and an inert, physiologically acceptable carrier.

The present invention further comprises a process for the preparation of the novel piperazine derivatives, which comprises condensing a substituted piperazine of the formula

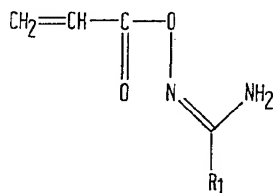


in which  $R_2$  has the above-stated meaning, with a 1,2,4-oxadiazole of the formula



in which  $R_1$  and  $n$  have the above-stated meanings.

The 1,2,4-oxadiazole starting materials for this process can be prepared by the process described by G Palazzo et al *J. Med. Pharm. Chem.*, 4, No. 2, (1961). In the case in which  $n$  is 2, it is preferred to use a variant of the above-described process in which the starting material is not a 1,2,4-oxadiazole but the corresponding acrylyl-amidoxime of the formula



in which  $\text{R}_1$  has the above-stated meaning, this compound being reacted with the appropriate substituted piperazine in an organic solvent, suitably toluene, at an elevated temperature.

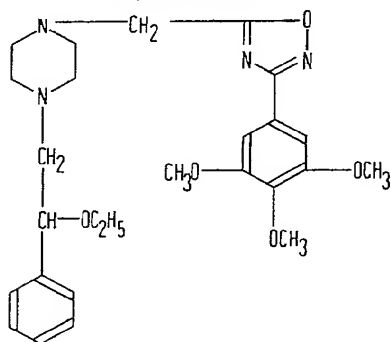
In order that the invention may be more fully understood, the following examples are given by way of illustration only:—

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## EXAMPLE 1

1 - (2 - Phenyl - 2 - ethoxy) - ethyl - 4 - [3 - (3,4,5 - trimethoxyphenyl) - 1,2,4 - oxadiazole(5)] - methylpiperazine dihydrochloride.

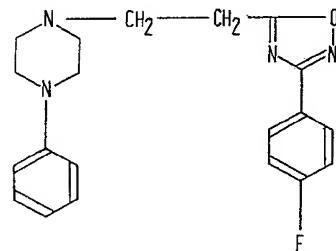
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23.4 g (0.1 Mole) of 1 - (2 - phenyl - 2 - ethoxy) - ethylpiperazine were heated for 2 hours under reflux with 28.55 g (0.1 mole) of 3 - (3,4,5 - trimethoxyphenyl) - 5 - chloromethyl - 1,2,4 - oxadiazole (m.p. 91—92°C) in the presence of 8.5 g of  $\text{NaHCO}_3$  and 150 ml of *n*-butanol. After cooling, the  $\text{NaCl}$  formed was filtered off and the butanol was evaporated *in vacuo*. The residue was taken up in absolute ethanol, the solution was filtered and acidified with  $\text{HCl}$ -saturated absolute ethanol. The dihydrochloride crystallised out. After two recrystallisations, the product was obtained as white crystals, m.p. 176°C.

## EXAMPLE 2

1 - Phenyl - 4 - { 2 - [ 3 - (4 - fluoro - phenyl) - 1,2,4 - oxadiazole (5) ] - ethyl } - piperazine.



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a) First stage: preparation of acrylyl - 4 - fluoro - phenyl - amidoxime.

110 g of 4 - fluoro - phenyl - amidoxime, 360 ml acetone and 60 g of anhydrous  $\text{K}_2\text{CO}_3$  were introduced into a 3-necked flask having a mechanical agitator, a thermometer, a  $\text{CaCl}_2$  tube and a bromine funnel. The flask was placed in an ice bath and a solution of 70 g of acrylic acid chloride in 80 ml of acetone was introduced into it with agitation and while maintaining the temperature between 5° and 10°C. Upon completion of the addition, the ice bath was removed and agitation was continued at ambient temperature for from 3 to 4 hours. Under these conditions there was partial precipitation of the product and the precipitate was washed with cold water. The remainder of the product was recovered by evaporation of the acetone. The two portions were combined and then washed first with cold 5% aqueous  $\text{Na}_2\text{CO}_3$  solution, and then with water. Crystallisation in acetone gave the required intermediate product, m.p. 99°—100°C.

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b) Second stage: preparation of end product.

10.4 g. (0.05 Mole) of acrylyl - 4 - fluoro - phenylamidoxime and 8.1 g of 1 - phenyl - piperazine were heated under reflux in the presence of 80 ml of toluene in a flask surmounted with a Dean-Stark decanter and an ascending condenser. Upon completion of the reaction as determined by the amount of water collected, which took about 5 to 6 hours, the toluene was evaporated off leaving a residue which crystallised. After two recrystallisations in ethanol, white needles of the end product were obtained, m.p. 101°C

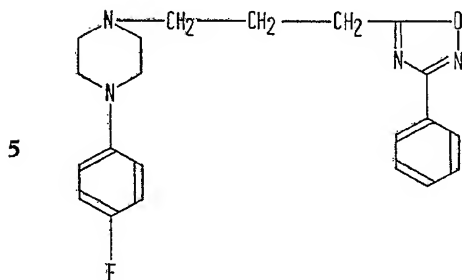
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## EXAMPLE 3

1 - (4 - Fluoro - phenyl) - 4 - { 3 - [ 3 - phenyl - 1,2,4 - oxadiazole (5) ] - propyl } - piperazine.

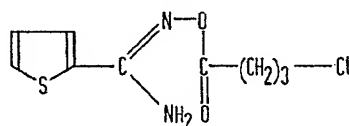


22.25 g (0.1 Mole) of 3 - phenyl - 5 - (3 - chloro - propyl) - 1,2,4 oxadiazole and 18 g (0.1 mole) of 1 - (4 - fluoro - phenyl) - piperazine were heated under reflux for 10 hours with agitation in the presence of 8.5 g of sodium bicarbonate and 151 ml of *n*-butanol. The NaCl formed was filtered off and after the solvent had been removed *in vacuo*, a thick oil was obtained which crystallised slowly. After two recrystallisations in methanol, white crystals of the desired product were obtained, m.p. 67°C.

## EXAMPLE 4

20 3 - (2 - Thienyl) - 5 - { 3 - [ 4 - (4 - fluoro - phenyl) - piperazine ] propyl } - 1,2,4 - oxadiazole dihydrochloride.

A. Preparation of 3 - chloro - butyryl - 2 - thienyl amidoxime



25 0.2 Mole of 2 - thienyl - amidoxime in 200 ml of acetone and 0.1 of anhydrous potassium carbonate were introduced into a 3-necked flask provided with a mechanical agitator, a thermometer, a CaCl<sub>2</sub> tube and a bromine funnel. The temperature was maintained at around 5°C while 0.22 mole of  $\gamma$  - chlorobutyryl chloride in 50 ml of acetone was added drop by drop. The mixture was agitated at ambient temperature for 2 hours, the precipitate was filtered off, washed first with ether and then with NaHCO<sub>3</sub> - saturated water. The amidoxime product was recrystallised in acetone; m.p. 120°C.

40 3 - Chloro - butyryl - 2 - furyl - amidoxime, m.p. 130°C. (dec.); 3 - chloro - butyryl - 3 - pyridyl - amidoxime, m.p. 125°C. (dec.); and 3 - chloro - butyryl - 4 - pyridyl - amidoxime, m.p. 130°C. were obtained similarly.

B. Preparation of 3 - (2 - thienyl) - 5 - (3 - chloro - propyl) - 1,2,4 - oxadiazole. 45

0.15 Mole of the amidoxime product prepared as described under heading A was heated under reflux in 100 ml of toluene in a flask provided with a Dean-Stark decanter and a reflux condenser. Upon completion of the reaction as determined by the quantity of water collected, the toluene was evaporated off and the residue was distilled *in vacuo* to give the desired 1,2,4 - oxadiazole, 55

b.p.<sub>2</sub> = 144°C  $n_D^{22} = 1.5670$

3 - Chlorobutyryl - 2 - furyl - amidoxime, 3 - chlorobutyryl - 3 - pyridyl - amidoxime, and 3 - chlorobutyryl - 4 - pyridyl - amidoxime were cyclised similarly to obtain the corresponding 1,2,4 - oxadiazoles, which are non-distillable products and are used in the crude state for the condensation reaction with piperazines. 60

C. Preparation of 3 - (2 - thienyl) - 5 - { 3 - [ 4 - (4 - fluoro - phenyl) - piperazine ] - propyl } - 1,2,4 - oxadiazole dihydrochloride. 65

0.1 Mole of the oxadiazole prepared as described above under heading B, 0.1 mole of 4 - (4 - fluoro - phenyl) - piperazine, and 0.11 mole of NaHCO<sub>3</sub> in 150 ml of *n*-butanol were heated under reflux for 10 hours. The mixture was filtered and the solvent was removed *in vacuo*. A residue was obtained which crystallised. The product, which was the free base, was recrystallised twice in methanol; m.p. 67°C. 70

N % calculated : 15.08  
N % found : 15.00 80

The dihydrochloride was prepared conventionally in absolute ethanol plus dry gaseous HCl. Recrystallisation is effected in ethanol, m.p. = 170°C.

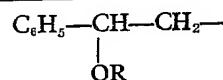
HCl calculated : 15.9  
HCl found : 18.85 85

All the compounds according to the invention and presented in Table I can be prepared by processes similar to those described. The dihydrochlorides can be prepared by the addition of HCl - saturated ethanol. 90

Table 1 of the accompanying drawings gives the meanings of the substituents R<sub>1</sub>, R<sub>2</sub> and *n* for a number of compounds according to the invention which have been prepared and lists the melting points of these compounds in their free base and hydrochloride forms. 95

The toxicity, anti-inflammatory, analgesic activity and other properties of compounds according to the invention have been evaluated by conventional test procedures, namely: 100

a) *Acute toxicity*: LD 50 *per os* in mice — BEHRENS and KARBER'S method (*Arch. Exp. Path. Pharm.*, 177, 379, 1935); results expressed in mg/kg.



5 b) *Analgesia*:

1. Thermal stimulus: methods of EDDY and LEIMOACH (*J. Pharm. Exp. Ther.*, 107, 385, 1953) and of CHEN (*Science*, 113, 631, 1951); results expressed in mg/kg (ED 50).

10 2. Chemical stimulus: methods of KOSTER (*Fed. Proc.*, 18, 412, 1959) and WITKIN (*J. Pharm. Exp. Ther.*, 133, 400, 1961); results (ED 50) expressed in mg/kg.

15 c) *Anti-inflammatory activity*: WILHELM and DOMENJOZ's method (*Arch. Forsch.*, 1, 151, 1951).

The results given are the planimetric values obtained by using does equal to 10% of the LD 50.

20 d) *General effects*: they were investigated for a 5 mg/kg intravenous dose in narcotised dogs:

25 X=study of the cardiomoderation caused by excitation of the peripheral end of the pneumo-gastric nerve.

A=study of the adrenalinic hypertension.

NA=study of noradrenalinic hypertension. (values expressed as percentage reductions).

30 e) *Action on central nervous system*: This was investigated by study of spontaneous motility using doses equal to 10% of the LD 50.

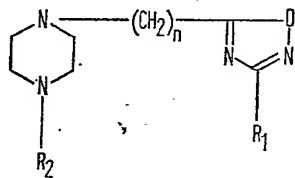
The results are expressed as follows:

35 + + + + 75 to 100% reduction  
+ + + 50 to 75% reduction  
+ + 25 to 50% reduction  
+ 1 to 25% reduction  
0 inactive.

40 All these results, evaluated for the 35 compounds of Table I, are combined and shown in Table II of the accompanying drawings.

WHAT I CLAIM IS:—

45 1. Piperazine derivatives of the formula



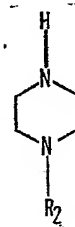
50 in which R<sub>1</sub> is a phenyl, 4-fluorophenyl, 3,4,5-trimethoxyphenyl, furyl, thienyl, 3-pyridyl or 4-pyridyl group; R<sub>2</sub> is a phenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, a phenyl-alkoxyethyl group of the formula

(in which R is an alkyl group containing 1 to 4 carbon atoms), or a benzyl group; and n is 1, 2 or 3, and their physiologically acceptable acid addition salts.

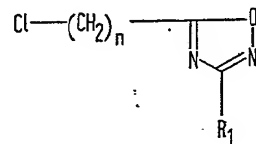
2. The compounds of the formula specified in claim 1 herein specifically described.

3. A pharmaceutical composition comprising one or more compounds as claimed in claim 1 or 2 and an inert, physiologically acceptable carrier.

4. A process for the preparation of piperazine derivatives of the formula specified in claim 1, which comprises condensing a substituted piperazine of the formula

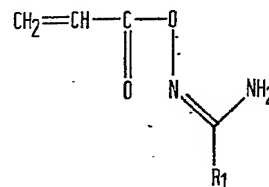


70 in which R<sub>2</sub> has the meaning specified in claim 1, with a 1,2,4-oxadiazole of the formula



in which R<sub>1</sub> and n have the meanings specified in claim 1.

5. A modification of the process claimed in claim 4 for the preparation of compounds according to claim 1 in which n is 2, in which the substituted piperazine is reacted with an acrylyl-amidoxime of the formula






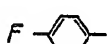



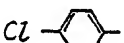

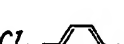

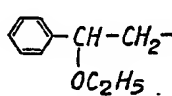

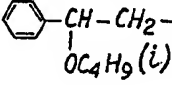


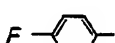


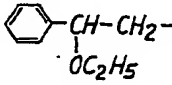
80 in which R<sub>1</sub> has the meaning specified in claim 1, in the presence of an organic solvent at an elevated temperature.

6. A process for the preparation of piperazine derivatives of the formula specified in claim 1 substantially as herein described in any of Examples 1 to 4.

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copies may be obtained.

TABLE I - EXAMPLES OF DE

COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF BASE (°C)	M.P. OF DI-HYDROCHLORIDE (°C)
1			3	—	148
2			3	67	160
3			3	72	168
4			2	112	172
5			3	81	172
6			1	—	158
7			3	—	166
8			3	—	182
9			2	101	161
10			1	—	153

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## COMPLETE SPECIFICATION

3 SHEETS

This drawing is a reproduction of  
the Original on a reduced scale

Sheet 1

## ES OF DERIVATIVES

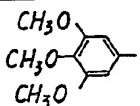

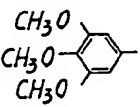

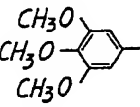
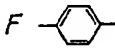
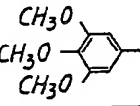

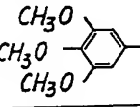
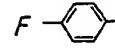
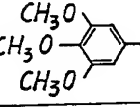

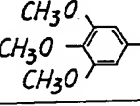
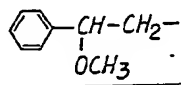
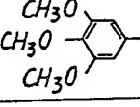
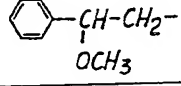
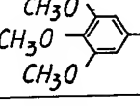
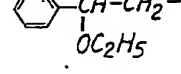
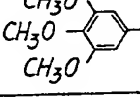
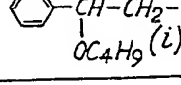
M.P. OF DI- HYDROCHLORIDE (°C)	COMPOUND No.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF BASE (°C)	M.P. OF DI- HYDROCHLORIDE (°C)
148	11			2	103	162
160	12			3	—	165
168	13			2	118	170
172	14			2	112	161
172	15			3	—	169
158	16			3	87	167
166	17			1	—	194
182	18			2	—	172
161	19			1	—	176
153	20			1	—	161

TABLE I - EXAMPLES OF DERIVATIVES






























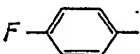

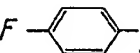

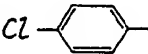

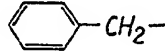

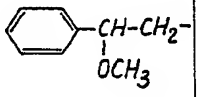

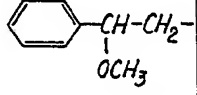
COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF DI- BASE (°C)	M.P. OF DI- BASE (°C)	R <sub>2</sub>	R <sub>1</sub>	COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF DI- BASE (°C)	M.P. OF DI- BASE (°C)
1			3	-	148			11			2	103	162
2			3	67	160			12			3	-	165
3			3	72	168			13			2	118	170
4			2	112	172			14			2	112	161
5			3	81	172			15			3	-	169
6			1	-	158			16			3	87	167
7			3	-	166			17			1	-	194
8			3	-	182			18			2	-	172
9			2	101	161			19			1	-	176
10			1	-	153			20			1	-	161



TABLE I (CONT

COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	<i>n</i>	M.P. OF BASE (°C)	M.P. OF DI-HYDROCHLORIDE (°C)
21			2		168
22			3	60	182
23			2		175
24			3	67	170
25			3	86	180
26			3	liquid	195
27			1		174
28			3		186

## LE I (CONTD.)






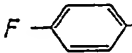
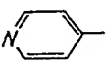


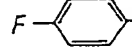



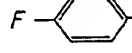
















M.P. OF DI- HYDROCHLORIDE (°C)	COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF BASE (°C)	M.P. OF DI- HYDROCHLORIDE (°C)
168	29			1	98	148
182	30			3		170
175	31			1	115	157
170	32			3		Trichlorhydrate 175
180	33			3		Trichlorhydrate 183
195	34			3	76	Trichlorhydrate 188
174	35			3	82	Trichlorhydrate 189
186						

TABLE I (CONTD.)

COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF BASE (°C)	M.P. OF DI- HYDROCHLORIDE (°C)
21			2		168
22			3	60	182
23			2		175
24			3	67	170
25			3	86	180
26			3	Liquid	195
27			1		174
28			3		186















COMPOUND NO.	R <sub>1</sub>	R <sub>2</sub>	n	M.P. OF BASE (°C)	M.P. OF DI- HYDROCHLORIDE (°C)
29			1	98	148
30			3		170
31			1	115	157
32			3		Trichlorhydrate 175
33			3		Trichlorhydrate 183
34			3	76	Trichlorhydrate 188
35			3	82	Trichlorhydrate 189

TABLE II  
PHARMACODYNAMIC EFFECTS OF THE DERIVATIVES OF TABLE I

COMPOUND NO.	ACUTE TOXICITY	ANALGESIA		ANTI-INFLAMMATORY ACTION	GENERAL EFFECTS			ACT. ON C.N.S.
		THERMAL STIM.	CHEMICAL STIM.		X	A	NA	
1	2500	110	150	328	—	INHIB.	INHIB.	++
2	1500	50	40	485	—	80	80	+++
3	2000	80	50	262	—	65	50	
4	>3000	i	—	172	—	60	50	++
5	>3000	140	175	365	—	—	—	0
6	3000	i	i	131	—	20	20	
7	>3000	—	200	286	26	15	—	
8	500	60	20	245	—	40	35	0
9	>3000	i	i	103	—	46	22	
10	1500	130	62.5	250	—	—	—	
11	>3000	425	110	160	—	INHIB	50	
12	>3000	75	50	359	—	INVERS.	60	++
13	>3000	i	—	137	—	60	50	
14	>3000	—	i	—	—	76	50	
15	2000		90	474	—	85	70	++
16	>3000	21	100	359	—	INV.	70	++

1110360

## COMPLETE SPECIFICATION

3 SHEETS

*This drawing is a reproduction of  
the Original on a reduced scale*

Sheet 3

12	> 3000	75	50	359	—	INVERS.	60	++
13	> 3000	i	—	137	—	60	50	
14	> 3000	—	i	—	—	76	50	
15	2000		90	474	—	85	70	+++
16	> 3000	31	100	359	—	INV.	70	+++
17	> 2500	100	110	—	—	—	—	
18	600	i	i	71	34	65	40	
19	> 3000	125	87,5	253	—	—	—	+++
20	> 3000	210	—	71	—	23	11	
21	1600	250	700	153	25	INV.	30	+++
22	> 3000	150	175	240	—	85	62	+
23	> 2000	—	30	203	—	70	42	+++
24	2000	120	30	367	—	30		
25	> 2000	100	175	174	28	80	80	+
26	415	—	i	i	—	40	—	++++
27	2000				40	30	—	+
28	> 1000	425	200		—	—	—	++
29	2500	—	—	137	78	—	—	
30	1300	—	80	279	—	83	60	
31	> 1000	—	—					
32	1500	—	25					+++
33	1000	37,5	15					++++
34	1500	100	40	392	—	79	43	++++
35	400	50	37,5	—	28	52	27	++++

PHARMACODYNAMIC EFFECTS OF THE DERIVATIVES OF TABLE I

COMPOUND NO.	ACUTE TOXICITY	ANALGESIA THERMAL STIM. CHEMICAL STIM.	ANTI-INFLAMMATORY ACTION	GENERAL EFFECTS			ACT. ON C.M.S.
				X -	A	NA	
1	2500	110	150	-	INHIB.	INHIB.	++
2	1500	50	40	-	80	80	+++
3	2000	80	50	-	65	50	++
4	>3000	I	-	-	60	50	++
5	>3000	140	175	-	-	50	0
6	3000	I	I	-	20	20	0
7	>3000	-	200	26	15	-	-
8	500	60	20	-	40	35	0
9	>3000	I	I	-	46	22	-
10	1500	130	62.5	-	-	-	-
11	>3000	425	110	-	INHIB.	50	++
12	>3000	75	50	-	INVERS.	60	++
13	>3000	I	-	-	60	50	++
14	>3000	-	I	-	76	50	++
15	2000	31	90	-	85	70	+++
16	>3000	100	100	-	INV.	70	+++
17	>2500	100	110	-	-	-	++
18	600	I	I	34	65	40	++
19	>3000	125	87.5	-	-	-	+++
20	>3000	210	-	-	23	11	+++
21	1600	250	700	25	INV.	30	+++
22	>3000	150	175	-	85	62	+
23	>2000	-	30	-	70	42	+++
24	2000	120	30	-	30	203	++
25	>2000	100	175	28	30	174	+
26	415	-	I	-	80	80	+
27	2000	425	200	40	40	40	++++
28	>1000	-	-	-	78	-	++
29	2500	-	-	-	-	-	+
30	1300	-	80	-	83	60	++
31	>1000	-	-	-	-	-	+++
32	1500	-	25	-	-	-	+++
33	1000	37.5	15	-	-	-	++++
34	1500	100	40	-	-	-	++++
35	400	50	37.5	-	-	-	++++

11110360 COMPLETE SPECIFICATION  
3 SHEETS This drawing is a reproduction of the Original on a reduced scale  
Sheet 3